



Market Opportunity and Future Industry Trends of Drug-Device and Biologic Combination Products

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Combination Products

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Outline

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Introduction

- Historic boundaries existed between devices and drugs
 - Devices – mechanical solutions to structural problems
 - Drugs – impact a biological process to effect an outcome
- Separate language, regulatory pathways, and business models

Introduction

Drug-device combinations can

- Improve a device's efficacy and/or safety through the use of a drug coating,
- Enable delivery of a drug to a specific site, or,
- Enhance the ease of delivery of drugs

Future Trends and Issues

- Medical device companies do not have the expertise to develop drugs
- Pharma companies are still focused on developing drugs
- Partnering will be the short-term solution to innovative device/drug combination products
- New companies are being established to capitalize on future opportunities

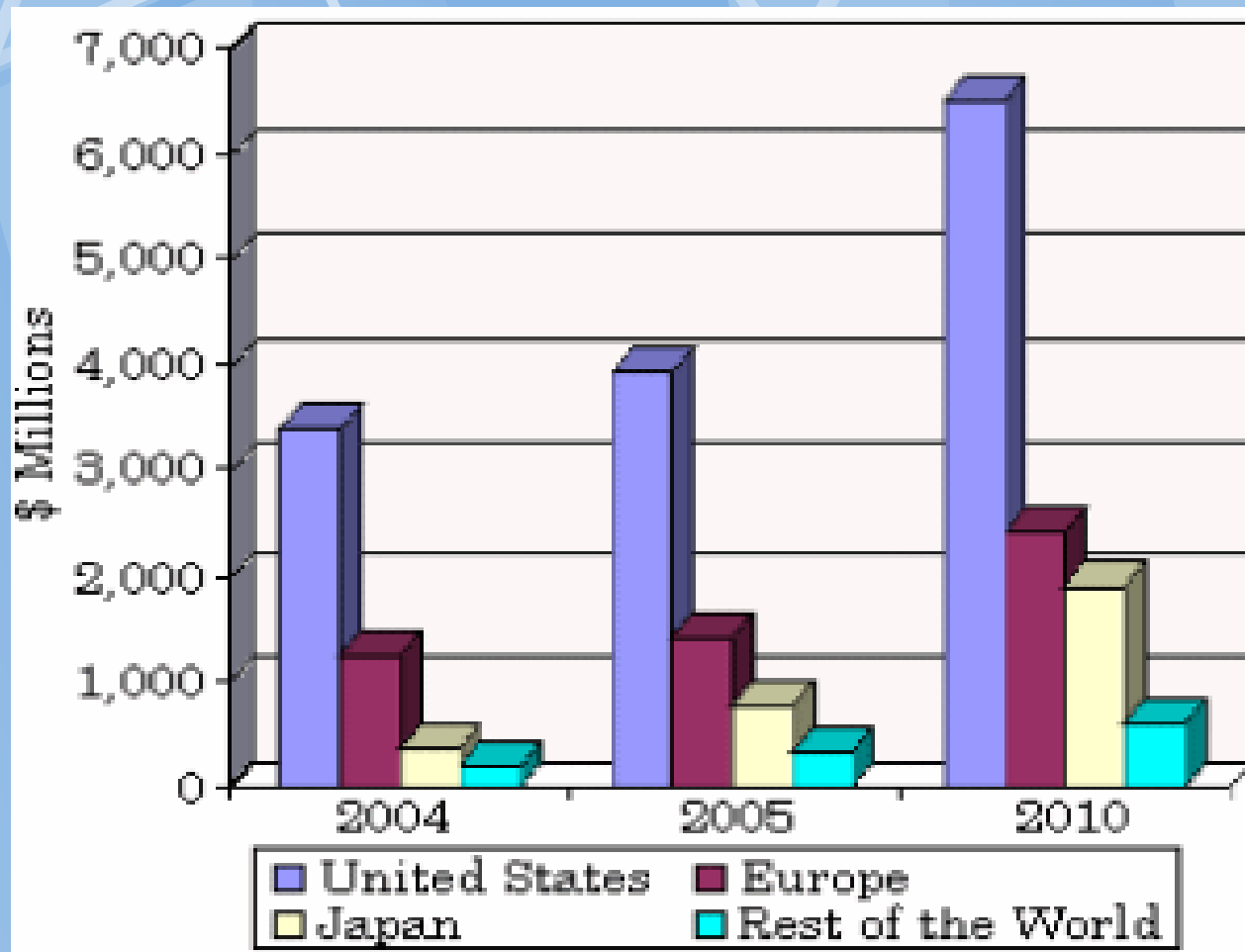
Technology Convergence in the New Organization?

- Drug design and development
- Device design and engineering
- Proteonomics and genomics
- Polymer science
- Information technology
- Nanotechnology

Evolution in drug-device combinations

- Inhalation Devices
- Transdermal Delivery Systems
- Prefilled syringes
- Insulin pumps
 - Pharmaceutical companies developed modified insulins more suitable for pumps
- Polymer implants and depot systems (e.g. Gliadel wafers)
- Drug Eluting Stents
 - Account for over 80% of the stents used within 3 years of introduction

Market for Drug Device Combination Products by Geographic Area, 2004-2010



Source: Business Communications Co, Inc

Market Projection for Drug-Device Combination Products

- \$5.4 billion in 2004 increasing to \$11.5b in 2010 (13.6 percent annual growth)
- Drug eluting stent market will reach \$8.0b in 2010
- Most categories will show double digit growth
- US dominates market

Technical Challenges

Combination of products introduces new issues:

- Drug release from polymer materials
- Local safety issues of drug and polymer
- Drug interaction with new contact materials
- Drug-device interactions
- Stability of the drug with the device
- Sterility for combination products
- Dose dumping from implanted systems
- Etc.

USA: Current Regulatory Process

- Office of Combination Products (OCP)
Created in 2002
- OCP will determine what are the issues that create potential risk to patient and assign primary review to:
 - CDER if risk of drug outweighs device
 - CDRH if risk of device outweigh those of drug

USA: Future Regulatory Trends

- Continuing Development of Rules and Guidelines
- Greater Authority for OCP

European Current Regulatory Process

- A product is regulated either as a Medical Device or Medicinal Product
- Key applicable Directives are:
 - Medical Device Directive 93/42/EEC
 - Medicinal Products Directive 2004/27/EC
- Assignment depends on intended purpose of the product and the method by which the principal intended action is achieved

European General Classification

- A device which is intended to deliver a medicinal product is regulated as a device
- The medicinal product in the device must be approved as a medicinal product
- If the device and medicinal product form a single integrated system, and is not reusable, the single product is regulated as a medicinal product (pre-filled syringes, asthma inhalers, transdermal patches)

European Possible Regulatory Trends

- Greater clarity in how combination products will be reviewed
- Increased requirements for Notified Bodies
- CE mark for medical devices separated from household items

Company Considerations in Development of a Drug-Device Combination

- Definition of synergistic possibilities
- Rigorous analysis of the market potential and customer acceptance
- Clear development strategy
- Early discussions with Regulatory Authorities
- Outcome benefits to justify reimbursement if associated with additional costs

Products that Enhance the Performance of Medical Devices

● Drug containing stents

- Projected to account for 70% of the combination product market in 2010
- Dramatic impact on restenosis (3% versus >11% requiring revascularization)

● INFUSE® bone graft

- Spinal fusion procedures for degenerative disc disease using BMP-2 on an absorbable collagen sponge in titanium fusion cages

Devices that Enhance Patient Acceptance of Drugs

- Single-use prefilled syringes
- Single-use autoinjectors
- Single-use needle-free injectors
- Inhalation devices to replace injection systems

Examples of Future Combination Products

- Controlled delivery of anti-arrhythmic drugs from tissue adherent polymeric hydrogel matrices (Genzyme)
- Insulin pump therapy with continuous glucose monitoring (Medtronic)
- Gliasite (Proxima Therapeutics) in cancer treatment – balloon catheter inserted after surgery and filled with a liquid radiation source

Advanced Therapy Medicinal Products

- **Evolving Opportunities**
 - Human Tissue Engineered products
 - Somatic cell therapy products
 - Gene therapy medicinal products
- **Within the European Community definitions in Article I of Directive 2001/83/EC and Article 3 of Directive 2004/23/EC**
- **Committee for Advanced Therapy Products established within EMEA**

Tasks for the Committee for Advanced Therapies

- To assess any data generated for an advanced therapy product and formulate an opinion
- At the request of the CPMP to formulate an opinion....
- To provide advice on any question related to advanced therapy products....
- To assist scientifically in elaboration of any document.....
- To provide scientific expertise and advice

Combined Advanced Therapy Medicinal Products

- An advanced therapy Medicinal Product which incorporates one or several medical devices within the meaning of Directive 93/42/EC, and which is liable to act upon the human body with action that cannot be considered as ancillary to that of the referred device(s)
- Any medical device which forms part of an advanced therapy medicinal product shall meet the essential requirements as laid down in Annex I to Directive 93/42/EC

Human Tissue Engineered Products

● Tissue Engineering

“The persuasion of the body to heal itself through the delivery to the appropriate sites of cells, molecular signals, and supporting structures” David Williams, 1999

● European Regulatory Initiatives

- Currently classified as Medicinal Products
- Human Cells and Tissue Directive (2004/23/EC)
 - Addresses donation, procurement and testing, not route to market
- Proposal for Community Regulatory Framework on Advanced Therapies (EC 04.05.2005)

● FDA

- CBER responsibility

Tissue Engineering Issues

- New development and regulatory challenges
- Organ transplant is not regulated
- Tissue banks not consistently regulated
- Business model to justify company investments

Commercial Potential for Tissue Engineered Products

- Current market approximately \$75m
- Future projection at \$290 to \$1.2b by 2013
- Challenges of cell sourcing, cell manipulation, tissue expression, implantation and incorporation, immune system response
- Concomitant use of scaffolds, growth factors, or genes?
- Definition of the product and who is the manufacturer will require consideration

Gene Therapy and Cell Therapy

- The introduction of genetic material into a cell to treat disease
 - Genetic diseases are caused by malfunctioning gene(s) – these can be inherited, occur at birth, or be randomly acquired owing to lifestyle or environmental factors
- Genes can be inserted into the affected tissue outside of the body, which is then returned, or delivered directly, typically using viral vectors

International Committee on Harmonization (ICH) and Gene Therapy

- Gene Therapy Discussion Group established with goals of:
 - Monitoring emerging scientific issues
 - Set out principles that could help in harmonizing regulations
 - Develop new ways of communicating to ensure outcomes of ICH are well understood

Progress Towards Market for Gene Therapy

- Gendicine for treating head and neck cancer approved in China in late 2003
- Other companies (e.g. Ark Therapeutics) are anticipated applications for market approval of their products in 2007
- Challenges remain in;
 - Gene delivery
 - Durability and integration
 - Immune response
 - Safety of vectors

Nanotechnologies

- Projected that in 10-15 years, \$1 trillion in products will be affected by nanotechnology
- Most things related to advanced materials, environment, energy conversion, and national security will be affected
- All materials and devices have their basic properties defined at the nanoscale

Mihail Roco, Director US National Nanotechnology Initiative

Potential Nanotechnology Applications

- *In vivo* “labs on a chip”
 - Nanotech biosensors and microfluidics to continuously monitor temperature, pulse, heart rhythm, blood pressure, oxygenation, glucose levels, detect pathogens, toxins, early tumors, etc.
- Enhancement of Medical Imaging
 - Nanotech particles coated with antibodies that bind to cancer cells
- Stronger artificial bone paste for repair and replacement in load bearing applications

The Near Future

- MEMS – Micro Electromechanical Systems (silicone wafers packed with information or drugs)
- Closed loop feedback delivery systems
- Nanobots capable of precise drug delivery or other intervention

(September 1999 – Cornell developed a nanobot 100,000X smaller than a grain of sand with small propeller with a segment of ATP attached)

The Future

- Miniscule particles that can travel through the body to detect and cure disease
- Chemotherapies that can attack individual cancer cells
- Artificial organs (e.g. pancreas)
- Artificial brain cell implants (Alzheimer's disease)
- Ability to repair damaged organs from the inside
- Self replicating machinery and self assembling medical products for eradication of acute and chronic diseases

Summary

- Numbers and types of combination products will continue to grow
- Earlier partnerships between device and drug companies likely
- Clearer, more predictable regulatory processes will evolve
- New technologies with the potential to revolutionize disease management will challenge current business models and reimbursements systems
- Continuing challenges from a regulatory perspective
- New types of companies likely to be created